Amendments to the Claims

This listing of claims replaces all prior versions, and listings, of claims in the above-identified application:

1. (Currently Amended) An isolated polynucleotide encoding a replication competent hepatitis C virus genotype 1a replicon ~~polynucleotide~~ comprising:

a 5' non-translated region (NTR), a 3' NTR, and a first coding sequence present between the 5' NTR and 3' NTR and encoding a hepatitis C virus polyprotein, wherein the polyprotein comprises an amino acid sequence having at least about 95% identity to SEQ ID NO:2, and wherein the amino acid sequence of the polyprotein comprises at least three adaptive mutations, wherein the adaptive mutations comprise an isoleucine at about amino acid 2204 [[,]] and ~~further comprises~~ at least two adaptive mutations selected from the group of an arginine at about amino acid 1067, an arginine at about amino acid 1691, a valine at about amino acid 2080, an isoleucine at about amino acid 1655, an arginine at about amino acid 2040, an arginine at about amino acid 1188, and a combination thereof~~, wherein the replication competent polynucleotide is isolated, wherein the amino acid sequence of the hepatitis C virus polyprotein and the amino acid sequence of SEQ ID NO:2 have at least about 90% identity, and wherein the 5' NTR, the 3' NTR, and the nucleotide sequence encoding the polyprotein are genotype 1a~~.

2. (Currently Amended) The isolated ~~replication competent~~ polynucleotide of claim 1 further comprising a second coding sequence.

3. (Currently Amended) The isolated ~~replication competent~~ polynucleotide of claim 2 wherein the second coding sequence encodes a marker.

4. (Currently Amended) The isolated ~~replication competent~~ polynucleotide of claim 2 wherein the second coding sequence encodes a transactivator.

5. Canceled

6. (Currently Amended) The isolated ~~replication competent~~ polynucleotide of claim 1 wherein the hepatitis C virus polyprotein is a subgenomic hepatitis C virus polyprotein.

7. (Currently Amended) The isolated ~~replication competent~~ polynucleotide of claim 1 wherein the hepatitis C virus polyprotein comprises cleavage products core, E1, E2, P7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B.

8. (Currently Amended) The isolated ~~replication competent~~ polynucleotide of claim 1 further comprising a nucleotide sequence having cis-acting ribozyme activity, wherein the nucleotide sequence is located 3' of the 3' NTR.

9-13. (Cancelled)

14. (Currently Amended) A method for making an isolated polynucleotide encoding a replication competent hepatitis C virus genotype 1a replicon ~~polynucleotide~~ comprising:

providing a polynucleotide comprising a 5' NTR, 3' NTR, and a first coding sequence present between the 5' NTR and 3' NTR and encoding a hepatitis C virus polyprotein, wherein the polyprotein comprises an amino acid sequence having at least about 95% identity to SEQ ID NO:2, and wherein the amino acid sequence of the polyprotein comprises a serine at about amino acid 2204, a glutamine at about amino acid 1067, a lysine at about amino acid 1691, a phenylalanine at about amino acid 2080, a valine at about amino acid 1655, a lysine at about amino acid 2040, or a glycine at about amino acid 1188 ~~and wherein the 5' NTR, the nucleotide sequence encoding the polyprotein, and 3' NTR are genotype 1a, wherein the amino acid sequence of the hepatitis C virus polyprotein and the amino acid sequence of SEQ ID NO:2 have at least about 90% identity~~; and

altering the coding sequence such that the polyprotein encoded thereby comprises at least three adaptive mutations, wherein the adaptive mutations comprise an isoleucine at about amino acid 2204[[,]] and at least two adaptive mutations selected from the group consisting of an arginine at about amino acid 1067, an arginine at about amino acid 1691, a valine at about amino acid 2080, an isoleucine at about amino acid 1655, an arginine at about amino acid 2040, an arginine at about amino acid 1188, and a combination thereof.

15. (Original) The method of claim 14 wherein the hepatitis C virus polyprotein is a subgenomic hepatitis C virus polyprotein.

16. (Original) The method of claim 14 wherein the hepatitis C virus polyprotein comprises cleavage products core, E1, E2, P7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B.

17. (Currently Amended) A replication competent hepatitis C virus genotype 1a replicon ~~polynucleotide~~ produced by the method of claim 14.

18. (Currently Amended) A method for identifying a compound that inhibits replication of a replication competent hepatitis C virus genotype 1a replicon ~~polynucleotide~~, the method comprising:

contacting a cell comprising a replication competent hepatitis C virus genotype 1a replicon ~~polynucleotide~~ with a compound, the replication competent hepatitis C virus genotype 1a replicon ~~polynucleotide~~ comprising a 5' NTR, 3' NTR, and a first coding sequence present between the 5' NTR and 3' NTR and encoding a hepatitis C virus polyprotein, wherein the hepatitis C virus polyprotein comprises an amino acid sequence having at least about 95% identity to SEQ ID NO:2, and wherein the amino acid sequence of the polyprotein comprises at least three adaptive mutations, wherein the adaptive mutations comprise an isoleucine at about amino acid 2204[[,]] and ~~further comprises~~ at least two adaptive mutations selected from the group of an arginine at about amino acid 1067, an arginine at about amino acid 1691, a valine at about amino acid 2080, an isoleucine at about amino acid 1655, an arginine at about amino acid 2040, an arginine at about amino acid 1188, and a combination thereof~~, wherein the amino acid sequence of the hepatitis C virus polyprotein and the amino acid sequence of SEQ ID NO:2 have at least about 90% identity, and wherein the 5' NTR, the 3' NTR, and the nucleotide sequence encoding the polyprotein are genotype 1a;~~

incubating the cell under conditions wherein the replication competent hepatitis C virus genotype 1a replicon ~~polynucleotide~~ replicates in the absence of the compound; and

detecting the replication competent hepatitis C virus genotype 1a replicon ~~polynucleotide~~, wherein a decrease of the replication competent hepatitis C virus genotype 1a replicon

~~polynucleotide~~ in the cell contacted with the compound compared to the replication competent hepatitis C virus genotype 1a replicon ~~polynucleotide~~ in a cell not contacted with the compound indicates the compound inhibits replication of the replication competent hepatitis C virus genotype 1a replicon ~~polynucleotide~~.

19. (Currently Amended) The method of claim 18 wherein detecting the replication competent hepatitis C virus genotype 1a replicon ~~polynucleotide~~ comprises nucleic acid amplification.

20. (Currently Amended) The method of claim 18 wherein the replication competent hepatitis C virus genotype 1a replicon ~~polynucleotide~~ further comprises a second coding sequence encoding a marker, and wherein detecting the replication competent hepatitis C virus genotype 1a replicon ~~polynucleotide~~ comprises identifying the marker.

21. (Currently Amended) The method of claim 18 wherein the replication competent hepatitis C virus genotype 1a replicon ~~polynucleotide~~ further comprises a second coding sequence encoding a transactivator, wherein the cell comprises a polynucleotide comprising a transactivated coding sequence encoding a detectable marker and an operator sequence operably linked to the transactivated coding sequence, wherein the transactivator interacts with the operator sequence and alters expression of the transactivated coding sequence, and wherein detecting the replication competent hepatitis C virus genotype 1a replicon ~~polynucleotide~~ in the cell comprises detecting the detectable marker encoded by the transactivated coding sequence.

22. (Original) The method of claim 18 wherein the cell is a human hepatoma cell.

23. (Original) The method of claim 18 wherein the hepatitis C virus polyprotein is a subgenomic hepatitis C virus polyprotein.

24. (Original) The method of claim 18 wherein the hepatitis C virus polyprotein comprises cleavage products core, E1, E2, P7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B.

25. Canceled

26. (Currently Amended) A method for selecting a replication competent hepatitis C virus genotype 1a replicon ~~polynucleotide~~, the method comprising:

incubating a cell in the presence of a selecting agent, wherein:

the cell comprises a polynucleotide comprising a 5' non-translated region (NTR), a 3' NTR, and a first coding sequence present between the 5' NTR and 3' NTR and encoding a hepatitis C virus polyprotein, and a second coding sequence, wherein the polyprotein comprises an amino acid sequence having at least about 95% identity to SEQ ID NO:2, and wherein the amino acid sequence of the polyprotein comprises at least three adaptive mutations, wherein the adaptive mutations comprise an isoleucine at about amino acid 2204[[,]] and ~~further comprises~~ at least two adaptive mutations selected from the group of an arginine at about amino acid 1067, an arginine at about amino acid 1691, a valine at about amino acid 2080, an isoleucine at about amino acid 1655, an arginine at about amino acid 2040, an arginine at about amino acid 1188, and a combination thereof~~, wherein the amino acid sequence of the hepatitis C virus polyprotein and the amino acid sequence of SEQ ID NO:2 have at least about 90% identity, and wherein the 5' NTR, the 3' NTR, and the nucleotide sequence encoding the polyprotein are genotype 1a~~;

the second coding sequence encodes a selectable marker conferring resistance to the selecting agent; and

the selecting agent inhibits replication of a cell that does not express the selectable marker; and

detecting a cell that replicates in the presence of the selecting agent, wherein the presence of such a cell indicates the polynucleotide is replication competent.

27. (Original) The method of claim 26 wherein the selecting agent is an antibiotic.

28. (Original) The method of claim 26 wherein the cell is a human hepatoma cell.

29. (Currently Amended) The method of claim 26 wherein the cell is a first cell, the method further comprising:

obtaining a virus particle produced by the first cell;

exposing a second cell to the isolated virus particle and incubating the second cell in the presence of the selecting agent; and

detecting a second cell that replicates in the presence of the selecting agent, wherein the presence of such a cell indicates the replication competent hepatitis C virus genotype 1a replicon ~~polynucleotide~~ in the first cell produces an infectious virus particle.

30. (Original) The method of claim 26 wherein the hepatitis C virus polyprotein is a subgenomic hepatitis C virus polyprotein.

31. (Original) The method of claim 26 wherein the hepatitis C virus polyprotein comprises cleavage products core, E1, E2, P7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B.

32. Canceled

33. (Currently Amended) A method for detecting a replication competent hepatitis C virus genotype 1a replicon ~~polynucleotide~~, the method comprising:

incubating a cell comprising a replication competent hepatitis C virus genotype 1a replicon ~~polynucleotide~~, wherein:

the replication competent hepatitis C virus genotype 1a replicon ~~polynucleotide~~ comprises a 5' non-translated region (NTR), a 3' NTR, and a first coding sequence present between the 5' NTR and 3' NTR and encoding a hepatitis C virus polyprotein, and a second coding sequence encoding a transactivator, wherein the polyprotein comprises an amino acid sequence having at least about 95% identity to SEQ ID NO:2, and wherein the amino acid sequence of the polyprotein comprises at least three adaptive mutations, wherein the adaptive mutations comprise an isoleucine at about amino acid 2204[[,]] and ~~further comprises~~ at least two adaptive mutations selected from the group of an arginine at about amino acid 1067, an arginine at about amino acid 1691, a valine at about amino acid 2080, an isoleucine at about amino acid 1655, an arginine at about amino acid 2040, an arginine at about amino acid 1188, and a combination thereof~~, wherein the amino acid sequence of the hepatitis C virus polyprotein~~

~~and the amino acid sequence of SEQ ID NO:2 have at least about 90% identity, and wherein the 5' NTR, the 3' NTR, and the nucleotide sequence encoding the polyprotein are genotype 1a;~~

the cell comprises a transactivated coding region and an operator sequence operably linked to the transactivated coding region; and

the transactivated coding region encodes a detectable marker, wherein the transactivator alters transcription of the transactivated coding region; and

detecting the detectable marker, wherein the presence of the detectable marker indicates the cell comprises a replication competent hepatitis C virus genotype 1a replicon ~~polynucleotide~~.

34. (Original) The method of claim 33 wherein the hepatitis C virus polyprotein is a subgenomic hepatitis C virus polyprotein.

35. (Original) The method of claim 33 wherein the hepatitis C virus polyprotein comprises cleavage products core, E1, E2, P7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B.

36. Canceled

37-40. (Cancelled)

41. (Currently Amended) A method for producing viral particles, comprising incubating a cell comprising the replication competent hepatitis C virus genotype 1a replicon ~~polynucleotide~~ of claim 1 under conditions allowing the polynucleotide to replicate.

42. (Original) The method of claim 41 further comprising isolating the viral particles.

43. (Original) A method for using the viral particles of claim 41 in an assay.

44-46. (Cancelled)

47. (Currently Amended) The replication competent polynucleotide of claim 1 wherein the replication competent hepatitis C virus genotype 1a replicon ~~polynucleotide~~ replicates in Huh-7 cells.

48. (Currently Amended) The method of claim 14 wherein the replication competent hepatitis C virus genotype 1a replicon ~~polynucleotide~~ replicates in Huh-7 cells.

49. (Previously Presented) The method of claim 22 wherein the cell is a Huh-7 cell.

50. (Previously Presented) The method of claim 28 wherein the cell is a Huh-7 cell.

51. (Previously Presented) The method of claim 33 wherein the cell is a human hepatoma cell.

52. (Previously Presented) The method of claim 51 wherein the cell is a Huh-7 cell.

53. (New) The isolated polynucleotide of claim 1 wherein at least three adaptive mutations are an isoleucine at amino acid 2204, an arginine at amino acid 1067, an arginine at amino acid 1691, a valine at amino acid 2080, an isoleucine at amino acid 1655, an arginine at amino acid 2040, and an arginine at amino acid 1188.